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(54) System for characterising a fluid, microfluidic device for characterising or analysing concentration components, a method of characterising or analysing such concentrations and a measurement device

(57) The present invention relates a system for characterising a fluid, comprising a microfluidic device and a measurement device, to the microfluidic device, to the measurement device, to the method of characterising or analysing a concentration of a component.

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Description

[0001] The present invention relates a system for characterising a fluid, comprising a microfluidic device and a measurement device, to the microfluidic device, to the measurement device, to the method of characterising or analysing a concentration of a component.

[0002] Analytic detection of particles, molecules and especially biomolecules, e.g., proteins, nucleic acids, hormones and the like, is fundamental to diagnostics as well as to molecular biology. In many applications, it is desirable to detect the presence of at least one particular molecule in a sample. Analytic detection is also used, e.g., in disease diagnosis and drug development, to determine the presence of a particular antibody or protein, e.g., in a blood sample or large chemical library. Detection of particles, molecules and biomolecules is therefore of fundamental value in, e.g., diagnostic medicine, archaeology, anthropology and criminal investigation. To meet these needs many techniques, e.g., DNA blotting, RNA blotting, protein blotting, and ELISA assays, have been developed to detect the presence of a particular molecule or fragment in the midst of a complex sample containing similar molecules.

[0003] More recently, new and faster microfluidic methods of performing biological assays in microfluidic systems have been developed, such as those described by the applications of Farce et al, "High Throughput Screening Assay Systems in Microscale Fluidic Devices" WO 98/00231 and in Knapp et al., "Closed Loop Biochemical Analyzers" (WO 98/45481; PCT/US98/06723). For example, high throughput methods for analyzing biological reagents, including proteins, are described in these applications.

[0004] Improved methods as well as the availability of fast, simple reliable and cheap detection systems for affinity assays are, accordingly, desirable, particularly those which take advantage of high-throughput, low cost microfluidic systems.

[0005] US-A-6,444,461 discloses integrated systems, apparatus, software, and methods are provided for performing biochemical analyses, including DNA sequencing, genomic screening, purification of nucleic acids and other biological components and drug screening. Microfluidic devices, systems and methods for using these devices and systems for performing a wide variety of fluid operations are provided. The devices and systems are used in performing fluid operations that require a large number of iterative, successive or parallel fluid manipulations, in a microscale, or sealed and readily automated format.

US-A-6,235,175 discloses microfluidic devices that incorporate improved recess and reservoir geometries, as well as methods of using these devices in the analysis, preparation, or other manipulation of fluid borne materials, to achieve higher throughputs of such materials through these devices, with lower cost, material and/or space requirements. It is mainly aimed at improved recess and reservoir geometries. This is necessary as the dimensions are relatively small, that is in the order of 1-100μm.

US-A-6,479,299 discloses microfluidic devices having predisposed assay components for increased throughput and prolonged shelf life. The methods involve flowing a first component of a biochemical system in a first of the at least two intersecting recesses. At least a first test compound is flowed from a second recess into the first recess whereby the test compound contacts the first component of the biochemical system. An effect of the test compound on the biochemical system is then detected. It uses electrokinetic flow.

US-A-6,613,581 discloses methods of detecting a component of interest, such as a protein, in a microfluidic system. The methods include the use of a component-binding moiety specific to the component of interest, such as an antibody, to detect the component of interest. Also included are microfluidic devices and integrated systems for performing such assays, including devices utilizing flowable or fixed particle sets.

US-A-6,644,944 discloses microfluidic fluid control devices. One microfluidic fluid control device can be used as a uni-directional valve within a microfluidic system. Said US- A-6,644,944 also teaches a microfluidic pump mechanism having two unidirectional valves separated by an expandable reservoir. Such devices may be formed in multiple layers and utilize flexible membranes.

US-A-6,408,878 discloses a method of fabricating an elastomeric structure, comprising: forming a first elastomeric layer on top of a first micromachined mold, the first micromachined mold having a first raised protrusion which forms a first recess extending along a bottom surface of the first elastomeric layer; forming a second elastomeric layer on top of a second micromachined mold, the second micromachined mold having a second raised protrusion which forms a second recess extending along a bottom surface of the second elastomeric layer; binding the bottom surface of the second elastomeric layer onto a top surface of the first elastomeric layer such that a control recess forms in the second recess between the first and second elastomeric layers; and positioning the first elastomeric layer on top of a planar body such that a flow recess forms in the first recess between the first elastomeric layer and the planar body.

US-A-6,086,740 discloses multiplexed microfluidic devices including a plurality of modular microfluidic elements, all of which are attached to a common frame or body, which itself includes one or more common input elements that are connected to corresponding input elements within several or each of the microfluidic modules for use in common control and/or common detection operations for each of the modules.

[0006] The state of the art is aimed at very small structures (containing typically less than 10 μl fluid). Disadvantages of such small structures are that fluids tend to clog and/or that upon flow bubbles in the fluid may be

formed.

[0007] Furthermore the volumes of samples and /or the constituents therein are often too large to flow through the small (nanoscale) structures. Not only impurities present in the sample but also components, such as red blood cells, tend to clog the structures and/ or hinder the flow severely.

[0008] Furthermore, it is clear that the fabricating techniques for very small structures are quite complicated.

[0009] Another disadvantage is that the body used does not comprise recesses on several of its surfaces, e.g. on both sides of a card-like body. This makes it difficult to separate or position functions, such as a pumping function from a chamber function.

[0010] A next disadvantage is that when electrokinetic flow is applied, it will typically function sub-optimally, that is the components do not flow according as intended. Amongst others electroosmotic flow interferes with the electrokinetic flow.

[0011] Another disadvantage is that the flow can not be controlled sufficiently, especially the amount of fluid to be flown as well as the velocity of the flow.

[0012] A next disadvantage is that the microfluidic devices of the state of the art are so small that they are difficult to handle.

[0013] A next disadvantage is that the characterisation of the components present in the microfluidic devices are difficult to be determined, as it is difficult to get access to components present and/or the measuring device to be used is not optimised for microfluidic devices.

[0014] Another disadvantage is that the microfluidic devices are relatively static systems. They allow for simple operations, that is typically reacting one fluid with another and typically only once.

[0015] Another disadvantage is that the microfluidic devices are in general not supplied with fluids, that may contain chemicals, and if so only a very limited set is present.

[0016] An additional disadvantage is that the microfluidic devices mentioned above are not dedicated to specific uses. For instance they do not contain a moiety to which a label or component present can be bound.

Detailed description of the invention

[0017] The present invention relates a system for characterising a fluid, comprising a microfluidic device and a measurement device, to the microfluidic device, to the measurement device, to the method of characterising or analysing a concentration of a component.

[0018] In a first embodiment the present invention relates to a system for characterising or analysing a fluid, which fluid is suspected to comprise at least one component to be characterised or analysed, comprising a microfluidic device, at least one pump for transporting the fluid and a measurement device which is arranged to characterise or analyse the fluid in use present in the microfluidic device,

which microfluidic device comprises at least one body (11), wherein the body has at least one surface, wherein the at least one surface has at least a part of the recess for containing the fluid in the microfluidic device and/or transporting the fluid in the microfluidic device through at least a part of the microfluidic device,

wherein the body has at least one provision for an inlet (15) and at least one provision for an outlet (18),

wherein at least a part of said recess (16) is a reaction chamber, which reaction chamber comprises a moiety that binds to the at least one component that is suspected to be present and that is to be characterised or analysed, which reaction chamber is arranged for characterising or analysing the at least one component,

wherein at least a part of said recess is a fluid connection (14) between the at least one provision for an inlet (15) and the at least one provision for an outlet,

wherein at least a part of said recess (17) is a pump chamber,

wherein at least the reaction chamber, pump chamber and fluid connection are sealed from the environment by at least one cover layer (12, 13).

[0019] A general layout of the microfluidic device is given in figure 1. It contains several recesses (14-17) on a body (11). The recesses are formed on both sides of the body. The fluid to be characterised or measured is brought into the provision for an inlet (15). Then, it flows to the reaction chamber (16). In the reaction chamber, a component that is suspected to be present can bind to a moiety, present in the reaction chamber (16). It further contains a pump chamber (17), which can be arranged to a pump (not visible). The pump forces the fluid to flow from the pump chamber to the reaction chamber or vice versa. The term "component" as used herein refers to a component that itself binds to a label or a moiety present in the microfluidic device, or to a chemical part of that component, of which at least one part binds to a label or a moiety present, or to a component which is labeled in the microfluidic device, which labeled component binds to the moiety present in the microfluidic device, or to a component that causes a detectable signal by itself, by a chemical reaction with another component, or by a component formed here out, whereby the detectable signal may be chemiluminescent flash or flow, colorimetric, fluorescent and time-resolved fluorescent.

[0020] The term "fluid" as used herein refers to liquid compositions that flow at operating pressure and temperature.

[0021] The term "pump" as used herein refers to a combination of an actuator, a displacement volume and at least one means for transferring the variation in pressure of the actuator towards the displacement volume. The means for transferring the variation can be a membrane. The displacement volume is referred to as pump chamber. The pump further comprises means for con-

trolling the actuator. The pump chamber typically has a volume of 1 -1000 µl, preferably of 10-100 µl.

[0022] The term "inlet" as used herein refers to a provision through which a fluid or a gas may pass. The direction of the fluid or gas is intended to be from the environment to a recess. It typically has a volume of 1-1000 µl, preferably of 1-10 µl.

[0023] The term "outlet" as used herein refers to a provision through which a fluid or a gas may pass. The direction of the fluid or gas is intended to be from a recess to the environment. It typically has a volume of 1-1000 µl, preferably from 1-10 µl.

[0024] The term "fluid connection" as used herein is a recess sealed by a cover layer. It is to be interpreted in a broad sense. Thus, it is not intended to be restricted to elongated configurations where the transverse or longitudinal dimension greatly exceeds the diameter or cross-sectional dimension. Rather, recesses are meant to comprise cavities and/or tunnels of any desired shape or configuration through which fluids may be directed. A cavity may, for example, comprise a flow-through cell where fluid is to be continuously passed or, alternatively, a chamber for holding a specified, discrete amount of fluid for a specified amount of time. A "fluid connection" may be filled or may contain internal structures comprising fluid diodes, valves or equivalent components. Its volume is from 1 to 1000 µl, preferably from 10-100 µl.

[0025] The term "microfluidic" as used herein is to be understood, without any restriction thereto, to refer to structures or devices through which fluid(s) are capable of being passed or directed, wherein one or more of the dimensions is less than 500 microns.

[0026] The term "recess" as used herein refers to a "fluid connection" type structure that is present on a surface of the body of the microfluidic device. The body substantially surrounds it. A recess in use is at least partly sealed by at least one cover layer, except for inlet and outlet provisions. It may also refer to part of a recess, especially in the case of chambers, meandering fluid path and fluid connection.

[0027] The term "chamber" as used herein refers to part of a covered recess in the body, which has a volume of 1-1000 µl, preferably of 10-100 µl. It is capable of for instance comprising a fluid, a binding-moiety etc. From the above it is clear that a chamber is also used as a fluid connection.

[0028] The term "reaction chamber" as used herein refers to a chamber used for reacting components and/or for binding at least one component to a moiety that is present in the reaction chamber. Furthermore, the reaction chamber can be arranged with the measurement device. It has a volume of 1-1000 µl, preferably of 10-100 µl, more preferably of 10-30 µl.

[0029] The term "meandering fluid path" as used herein refers to part of a fluid connection. It is a channel type part of a recess, which channel forms several bends. Hereby a relatively long channel occupies only a limited amount of surface on the microfluidic device. It has a volume of 1 -1000 µl, preferably of 10-500 µl, more preferably of 50-200 µl.

[0030] The term "body" as used herein refers to a solid material. The solid material has at least one surface and can be of any shape. A preferred shape has the dimensions of a "credit-card". At least one surface of the body comprises at least a part of a recess. In a preferred embodiment of the present invention the top and bottom side of the body comprise at least one recess. The at least one recess of the topside is in fluid connection with the at least one recess of the bottom side. The solid material should allow for manufacturing techniques to form recesses on the surface of the body. Such manufacturing techniques are for instance moulding, injecting moulding, hot embossing and lithographic processes, optionally combined with etching techniques. Further, the material preferably is stable and chemically resistent to the fluids used in the microfluidic device. It furthermore preferably has the desired physical properties, such as hydrophilicity and a smooth surface after manufacturing. The material used as body is typically a polymer or silicon or glass. A suitable polymer is selected from the group consisting of latex, rubber, polyesters, polycarbonates, polyalkanes, polyalkenes, polytetrafluoroethylenes, polypropylenes, polyimides, polymethylmethacrylates, silicones, polymethylmethacrylate (PMMA), PEEK, polystyrene, PDMS, and polyesters. A preferred material is polymethylmethacrylate (PMMA).

[0031] The term "cover layer" as used herein refers to a material that is used to seal recesses from the environment. The material used as cover layer is typically a polymer or silicon or glass. A suitable polymer is selected from the group consisting of latex, rubber, polyesters, polycarbonates, polyalkanes, polyalkenes, polytetrafluoroethylenes, polypropylenes, polyimides, polymethylmethacrylates, silicones, polymethylmethacrylate (PMMA), PEEK, polystyrene, PDMS, and polyesters. A preferred material is polymethylmethacrylate (PMMA).

[0032] Typically the moiety that binds a component is attached to the cover layer, covering the reaction chamber. This has the advantage that the moiety can be deposited on the cover layer, prior to covering the reaction chamber recess with this cover. In figure 2 this configuration is shown. The cover layer (12) has an adhesive (22) to which the moiety (23) is attached. The reaction chamber itself (16) is a recess in the body (11). Further, a second cover layer (13) is visible. In another embodiment the moiety can be present in the form of magnetic and/or non-magnetic antibody coated particles. The moiety that binds is chosen from the group consisting of a nuclear receptor, an intracellular receptor, a solubilized receptor, an antibody, an antigen, an enzyme, avidin, a polynucleotide and a polysaccharide.

[0033] In many of the above described embodiments it has been a goal to miminise the dimensions. The inventors of the present invention have found however

that such a minimization encompasses all sorts of problems, such as clogging, bubble-formation, manufacturing problems and so on.

[0034] The present invention has a first advantage that it can optimally use the surface of the body, e.g. both sides of a credit-card shaped body, to form recesses. This makes it possible to separate various functions of the system, such as the pump function and the receiving function. In a preferred embodiment of the invention the energy transfer (pump function) is located at one side of the body and the provision for an inlet and the reaction chamber are located on the other side. The pump function generally requires a relative large amount of space, even with the micro-sized pumps that now become available.

[0035] The present invention is not particularly aimed at reducing the size; it rather provides a microfluidic device that is easy to operate. For instance in a preferred embodiment of the invention the microfluidic device has size of that is similar to that of a credit card, e.g. 85 by 60 by 1 mm^3.

[0036] The present invention further has the advantage that it provides a combination of a microfluidic device with a compatible measurement device. For instance the microfluidic device is filled with a fluid to be characterised or analysed. After the pump forces the fluid to flow from the pump chamber to the reaction chamber, the fluid can be characterised by the measuring device by arranging the microfluidic device with the measuring device.

[0037] In a preferred embodiment the system of the invention comprises a measurement device for characterising the fluid, wherein the measurement device is arranged to obtain information based on an optical technique selected from the group consisting of fluorescence, chemiluminescence, time resolved fluorescence, time resolved chemiluminescence, colorimetry or a combination thereof, or from the group consisting of magnetic measurements, resistivity measurements, capacity measurements, surface plasma resonance (SPR) measurements, or a combination thereof. This embodiment has the advantage that the measurement device can easily be arranged to the microfluidic device. A preferred embodiment radiates the reaction chamber and detects emitted radiation. An optical measurement device is arranged to obtain information based on a technique selected from the group consisting of fluorescence, chemiluminescence, time resolved fluorescence, or a combination thereof. A preferred embodiment uses a fluorescence technique.

[0038] In another embodiment the system of the invention characterises the concentration of at least one component present in the fluid. Preferably it is used to characterise one component, which has the advantage that the system can be fully optimised to characterise this one component. For instance the moiety present in the reaction chamber, the wash fluid, the detection are optimised. It provides microfluidic devices comprising all necessary material in the device.

[0039] In a preferred embodiment the system of the invention comprises at least one pump. This pump can be present on the microfluidic device or in the measurement device. Preferably this pump is a piezo-pump. The present invention makes use of a piezo pump in a structure, which has as further advantage that it enables the fluid to be directed from a part of the recess to another recess. The present invention further uses the piezo pump in order to perform all kinds of pumping functions, for instances to move fluids in controlled amounts form a part of the recess tot the other, to perform pumping cycles, to optimise piezo frequencies with respect to the dimensions of the recesses, to permit time intervals in between pumping etc. The at least one piezo-pump preferably operates at a frequency up to 40 kHz. The frequency may also be used to reverse the preferred flow direction of the fluid diode. The man skilled in the art will appreciate the possibilities of such a pump and will apply the pump in such a way to fulfil the requirements of the specific application.

[0040] In another embodiment the system is disposable all together. In extreme situations, such as emergency or war, there may be a need to identify the status of a patient on short notice, whereas the desire to maintain the measurement device is not an issue. Such a disposable system has in such a situation the advantage of providing a dedicated and quick answer to the status of a patient.

[0041] In a next embodiment of the invention a microfluidic device arranged for use in the system of the invention is used, which microfluidic device comprises at least one body (11), wherein the body has at least one surface, wherein the at least one surface has at least a part of the recess for containing the fluid in the microfluidic device and/or transporting the fluid in the microfluidic device through at least a part of the microfluidic device,

wherein the body has at least one provision for an inlet (15) and at least one provision for an outlet (18),

wherein at least a part of said recess (16) is a reaction chamber, which reaction chamber comprises a moiety that binds to the at least one component that is suspected to be present and that is to be characterised or analysed, which reaction chamber is arranged for characterising or analysing the at least one component,

wherein at least a part of said recess is a fluid connection (14) between the at least one provision for an inlet (15) and the at least one provision for an outlet,

wherein at least a part of said recess (17) is a pump chamber,

wherein at least the reaction chamber, pump chamber and fluid connection are sealed from the environment by at least one cover layer (12, 13).

[0042] In a preferred embodiment of the microfluidic device two cover layers form one part, which make it easier to seal the microfluidic device. This is an advantage in the manufacture of the microfluidic device.

[0043] In a next embodiment of the microfluidic device it further comprises a filter in at least one provision for an inlet. The filter is used to hold particles and/or components that adversely interfere in the characterisation or analyses of the fluid in the measurement device. The filter is for instance a particle filter, such as a Millipore™ filter with an intended hole-size, or a chemical compound that reacts or binds to undesired components, thereby immobilising these components.

[0044] In a next embodiment of the microfluidic device it further comprises at least a part of the recess for a washing fluid and at least a part of the recess for collecting waste fluid. This has the advantage that after moving the fluid from the provision for an inlet to the reaction chamber and after reaction in the reaction chamber, the reaction chamber is washed with a washing fluid. Hereby is the reaction chamber cleaned, which has the advantage that the subsequent measurement is not or less adversely effected by other components present in the fluid to be characterised.

[0045] In a next embodiment of the microfluidic device it further comprises at least a part of the recess which comprises at least one label fluid, which label binds to the moiety in the reaction chamber and/or to the at least one component to be characterised or analysed. In figure 3 such a layout is given. It shows a top view of the microfluidic device. It should be noted that the bottom side of the microfluidic device comprises also a number of recesses. The bottom side is brought into an arrangement with the pump-actuator. A first glance at the figure immediately indicates the intense use of the surface of the body. Not only do reaction chamber(s) occupy space, but also the meandering fluid path type recesses do. These meandering fluid path type structures have the advantage that they contain a relative large volume on the side, which is combined with the possibility to flow very well controlled amounts of fluid on the other side. In a preferred embodiment a meandering fluid path type structure contains from 1-1000 µl of fluid. A further advantage with respect to a chamber is that the meandering fluid path can be emptied almost completely, whereas a chamber always has some residual liquid. Further, the meandering fluid path has less leakage as compared to a chamber. The fluid to be characterised is transferred to the provision for an inlet (15). This provision for an inlet is in fluid connection with the central reaction chamber (16). It is optional to have other reaction chambers present (16), which serve similar functions as the first chamber. Not visible in the layout of figure 3 are various measures taken to improve the flow of the fluid to be characterised and analysed and the other fluids used. These measures are amongst others a special design of the provision for an inlet and of the fluid connection between the provision for an inlet and the reaction chamber, as well as measures taken to improve the fluid flow in reaction chamber. This has the advantage that the fluids in the reaction chamber mix better, thereby improving the reaction-rate and minimising the required amount of fluid to the obtained an intended result. The recesses that contain wash fluid, label fluid, sample fluid (fluid to be characterised or analysed) and waste fluid are associated with a pump, such as a piezo-pump. The fluid flows through one of the fluid connections. The provision for an inlet (15) is used to insert the fluid to be characterised or analysed. Fluid connections (33-35) are used to transfer the label fluid. Fluid connections (36-38) are used to transfer the wash fluid. Fluid connection (39) is used to collect the waste fluid. This embodiment has the advantage that it comprises all necessary fluids in one single body. Furthermore the fluid connections and the arrangement of the pump enable complicated reaction sequences, involving one or more label steps and one or more washing steps.

[0046] In figure 4 another layout is given. The dimension of this layout is 60 mm by 49 mm. The recess on the bottom surface as well as the contact area of the pump actuator is projected onto the front side. Figure 4 shows a provision for an inlet (15), wherein the fluid to be characterised or analysed is injected. The fluid is moved from the inlet (15) towards the reaction chamber (16) by means of a pump (17), located on the bottom side, in fluid connection with the front side. The fluid diodes (40) provide for the desired flow direction of the fluids used. Further visible are meandering fluid path type structures (14) containing other fluids, such as washing fluid and label fluid. These fluids are directed towards the pump chamber by means of the pump. Thereto the at least one provision for the outlet (18) is opened, in order to compensate for the volume of fluid moved. The design of the provision for the inlet and the fluid connection towards the reaction chamber limit the back flow. The design of the reaction chamber is such that it provides for optimal flow profiles, with minimised dead volume and optimised contact with the moiety present. Furthermore a large meandering fluid path is present for collecting the waste fluid from the reaction chamber. Also visible are fluid connections (19) between the bottom side and the top side of the microfluidic device.

[0047] The term "label" as used herein refers to a compound that can be detected directly or indirectly by the measuring the device. So it can also be a particle containing a label, such as a 3-dimensional structure with a label inside. Or it may be an enzyme that first may react with another component present. It also can form a bond with the moiety and/or at least one of the components present in the fluid. Preferred one or more of the following typically characterizes labels: high sensitivity, high stability, causing a low background signal upon detection, low environmental sensitivity and high specificity in labelling.

[0048] A preferred embodiment of the microfluidic device further comprises at least one provision for an inlet (15) which is arranged to receive the fluid, said inlet being sealed by a seal from the environment, which seal

is to be removed upon use, thereby opening at least one entrance to the at least one provision for an inlet and/or which comprises at least one provision for an outlet (18) that is prior to use sealed from the environment by a seal, which seal is to be removed upon use. This has the advantage that the microfluidic device has a prolonged shelf life. Typically the at least one provision for an outlet and the least one provision for an inlet will also be opened prior to use, the first to enable a fluid to flow, the latter to enable a sample to be inserted into the microfluidic device. This has the advantage that the microfluidic device has a prolonged shelf life. Furthermore it is ready to use. And it can be used once and then disposed of. As it comprises a minimal amount of fluids the environmental impact is small. A preferred embodiment of the microfluidic device further comprises at least one soft seal that closes at least a part of the recess.

[0049] The term "soft seal" as used herein refers to a seal that closes a part of the recess, thereby preventing liquid and/or gas to flow from this apart to another part. The soft seal is broken upon applying a limited amount of force, such as the pressure or energy transferred by a pump. Typically the soft seal is selected from the group of fluids with relatively high viscosity. Soft seal material can e.g. be selected from the group of silicones and silicone oils. The advantage of such a seal is clearly that is prevents leakage, not only in normal circumstances, but also for instance during transport of the device.

[0050] A preferred embodiment of the microfluidic device characterized in that at least one of the fluid connection(s) is equipped with fluid diodes for resisting a flow of the fluid through the fluid connections in one direction. This fluid diodes (40) are also shown if figure 3. A clear advantage of the use of such diodes it that it directs the flow of fluids in a desired direction, whereas it reduces the flow in the other direction significantly. This has the further advantage that it enables the performance of more complicated reaction programs. Furthermore in these reaction programs or reaction schemes various fluids can be used, whereas without the diodes this would be much more complicated or even impossible. A further advantage is that it allows for much more complex structures on (both sides) of the body, whereby many more fluid connections are made, without the fluids being undesirably mixed or flowed. A further advantage is that recesses and/or chambers that comprise different fluids can be separated if required in one flow direction.

[0051] The term "fluid diode" as used herein refers to a structure within a recess, which is characterized in that the resistance to a fluid flow is significantly larger in one direction compared to the other and which has no moving parts. In other words, the resistance towards a fluid flow changes significantly with change in the direction of the flow. It further has the advantage that applying a different frequency from the actuator of the pump may reverse the preferred flow direction. In a preferred embodiment the fluid diodes have a brush-like or valve-like structure. The proper orientation of the brush structures is not intuitively obvious even to one skilled in the art. It rather must be determined with mathematical modelling of the fluid flow and by experimentation. Figure 5 shows top view of a preferred embodiment of a fluid diode in a body (11). The recess (14) contains brush like structures (51), which act as a resistance to the flow in one direction. The arrow (53) indicates the flow direction that is not hindered. In that case, the fluid enters the fluid diode indicated with (52). The fluid diode has a width of 1 mm. The brushes are 0,5 mm long and 70 μm wide.

[0052] In a next embodiment of the microfluidic device it further comprises further elements for directing the fluid. Such elements are for instance valves. This has the advantage that even more complex pumping operations and reaction sequences can be performed.

[0053] In yet another embodiment the microfluidic device further comprises a readable information carrier. In a preferred embodiment the readable information carrier is an optically or electrically readable information carrier, most preferably it is an electrically readable information carrier. The information carrier may be detachable from the microfluidic device. As for example in emergency situations a measurement would be performed, thereby using a microfluidic device according to the invention. The result of the measurement may need to be logged into a central computer; therefore the results need to be transferred from the microfluidic device to the computer. The device itself may be contaminated and therefore needs to be disposed. A detachable information carrier thus allows for the desired transfer. The readable information carrier contains data that is for instance relating to the microfluidic device and/or relating to a method of operating the microfluidic device and/or the system for characterising a fluid. It further provides operating instructions, such as pump frequencies. These instructions optimise the use of materials contained in the device, the time necessary to label the components of interest, the accuracy of the result obtained. It also provides measurement instructions, such as a pump times, intervals etc. It also contains data relevant to the device, such as intended use, and it contains data relevant to the measurement, such as type of device and calibration curve respectively. In another embodiment the information carrier just provides the measurement system with the intended use. This reference allows the measurement system then to retrieve and/or calculate the above-mentioned data and use it accordingly. This information present in the information carrier has the advantage that the use of the microfluidic device, in combination with the measurement device is very easy and can be performed by persons with limited skills and knowledge.

[0054] In a further embodiment the microfluidic device further comprises labels. In a preferred embodiment these labels are selected from fluorescent labels, chemiluminescent labels and colorimetric labels.

[0055] In a first embodiment the measurement device

suitable for use in a system characterises a fluid in the microfluidic device of the present invention, which fluid is suspected to comprise at least one component to be characterised or analysed, which measurement device is associated to the microfluidic device Figure 6 represents a schematic layout of the actual detection in the measurement device. A light source (41) is used to radiate (42) a component present in the reaction chamber (16). In the figure the light source is a laser. In order to optimise the radiation a lens (43) may be used. If a component is present in the reaction chamber (16) that emits radiation (45), this radiation can optionally be passed through a filter (46). In the figure it is assumed that the component is or comprises a fluorescent label. If light is emitted it is detected by a detection unit (47).

[0056] In a second embodiment the measurement device further comprises, at least one communication port for transferring data, at least one read-out unit for reading in characteristics of the microfluidic device, at least one light source illuminating the reaction chamber in the microfluidic device, at least one detection element for detecting the radiation emitted from the reaction chamber, an information unit displaying characteristics of the fluid. This measurement has the advantage that it is simple in use in combination with the microfluidic device of the invention and can be performed by persons with limited skills and knowledge. Furthermore the measurement device itself is simple and can be constructed easily. It further contains no expensive elements, which allows for the measurement to be very economical. It further makes use of readily available elements, which makes the manufacture of it easy, economical and reliable. It also has the advantage that the result of a measurement is available within a limited amount of time. Typically a measurement from start to finish takes 1-15 minutes. The results can be transferred to a data-collecting system, such as a computer, using the communication port. The read-out unit allows for the information relating to the microfluidic device and the type of measurement to be transferred to the measuring device and subsequently to the data-collecting device, without any burden. The information safeguards the correct use of the measurement device and therefore also of the results obtained. The unit that is associated with the microfluidic device furthermore provides for a simple to perform measurement.

[0057] The information unit provides for the opportunity to directly obtain a visual result that can be used in a subsequent action, such as treatment.

[0058] The measurement device will typically be used to characterise or analyse a component that is selected from the group consisting an antibody, a cell receptor, an antigen, a receptor ligand, an enzyme, a body, an immunochemical, an immunoglobulin, a virus, a virus binding component, a protein, a cellular factor, hormones, allergenics, a growth factor, an cell-inhibitor, DNA, RNA, antigen to be bound to an antibody or receptor or a combination thereof

[0059] In a further embodiment the measurement device further comprises a communication port of an USB-type. This is a standard interface for electronic devices, which allows for easy installation and easy data transfer. And it is economical.

[0060] In another embodiment the measurement device further comprises a chip-reader as the read-out unit. This is a standard interface for reading information on chips, which allows for easy installation and easy data transfer. Typically the read-out unit can also be used to write data on the chip. This data comprises the result or results of the characterisation or analysis. This has the advantage that the information can later on be logged, for instance to a central computer facility. It can further comprise sample information and patient information. And it is economical.

[0061] In a further embodiment the measurement device further comprises a laser as the light source. A laser has the advantage of emitting nearly monochromatic light, though an option may be to use polychromatic (laser) light and use filters. The latter is preferably used in the case that the measurement device has a multipurpose use and/or is used to detect various wavelengths of emitted light at the same time. Also a laser can be easily replaced if necessary. It also is a reliable light source that consumes a low amount of energy.

[0062] In a further embodiment the measurement device comprises a photodiode, a CCD, a photo multiplier tube (PMT) or a series of photodiodes as the detection element. The detection element is capable of detecting the light that is emitted by the at least one component to be characterised or analysed. The advantage of photodiodes or CCD is that they are quite specific with respect to the wavelength chosen.

[0063] In a further embodiment the measurement device further comprises software. The software is used for at least directing the at least one pump to transfer an external pressure to at least one of the chambers of the microfluidic device of the invention. The software further provides for the information on the microfluidic device to be transferred to the measurement device and subsequently to perform the reaction sequence. It provides for the determination of the concentration of the at least one component suspected to be present in the fluid. It therefore provides for a simple operation procedure and minimises the risk for mistakes.

[0064] Also the measurement device may comprise a local memory and/or computing chip, in order to store and retrieve data as well as to perform calculations and to control the other components present.

[0065] For the man skilled in the art it is a routine job to construct such a measurement device out of widely available parts.

[0066] Further the invention describes a method for characterising or analysing characterising or analysing at least one component that is suspected to be present in a fluid comprising,

a. introducing a fluid to be characterised or analysed in a microfluidic device according to the invention,
b. moving the fluid to a reaction chamber,
c. reacting the fluid with the moiety that binds,
d. moving a washing fluid to the reaction chamber and washing the reaction chamber,
e. illuminating the reaction chamber to a light source emitting radiation,
f. detecting the radiation emitted.

[0067] Typically, the method comprises separating a mixture of components, which mixture of components may contain the components of interest. To detect the component of interest, the mixture of components or the separated components are contacted to a component-binding moiety specific to the component of interest. The component-binding moiety binds to the component of interest and is detected, thereby detecting the component of interest, either by measuring the component-bonding moiety directly or by measuring the result of competition with other components, that have been replaced by the component of interest. The embodiment of the present invention has the further advantage that the complete procedure can be performed on one microfluidic device and the measurement result can be obtained directly from the measurement device associated with it.

[0068] In a second embodiment for a method for characterising or analysing characterising or analysing at least one component that is suspected to be present in a fluid comprising,

a. introducing a fluid to be characterised or analysed in a microfluidic device according to the invention,
b. moving the fluid to a reaction chamber,
c. reacting the fluid with the moiety that binds,
d. moving a label fluid to the reaction chamber and reacting the label with the moiety that binds and/or with the component to be characterised or analysed,
e. washing the reaction chamber with a washing fluid,
f. illuminating the reaction chamber to a light source emitting radiation,
g. detecting the radiation emitted.

[0069] In this embodiment, a component of interest is labelled with a detectable label, subsequently bound to the binding moiety and then detected. The detection signal is then calculated to a concentration, using a calibration curve of the label.

[0070] In a preferred embodiment the microfluidic device is in arrangement with a piezo-pump. The piezo-pump is instructed to perform complicated pumping cycles, involving pumping a fluid, leaving the fluid to react and repeating such steps. In a further embodiment complex pumping cycles of one fluid are alternated with complex pumping cycles of another fluid. For instance, first a label fluid is moved to the reaction chamber with such a pumping cycle and subsequently a wash fluid, which steps are repeated if required. This clearly has the advantage that the reaction in the chamber can be optimised by controlling the amount of fluid moved to the reaction chamber. This is important as the reaction is mainly determined by fluid dynamics. By supplying an amount of fluid each time the fluid dynamics cause exhaustion, the reaction rate is significantly enhanced. Therefore the reaction rate is to a large extend determined by the kinetics of the pumping, rather than by the movement of components in the fluid due to concentration gradients. This improves the reaction time as well as the sensitivity. A further advantage is that the amount of fluid used are minimised with such a procedure. This has the further advantage that even more complicated pumping operations and reaction sequences can be performed.

[0071] In another embodiment the moiety can be present in the form of (magnetic and/or non-magnetic antibody) coated particles. The particles are optionally stacked in a detection region. The component-binding moiety thereby binds to the component of interest, thus providing detection of the component of interest.

[0072] In a further aspect, the method comprises providing a body structure having a plurality of recesses disposed therein, the plurality comprising a microfluidic separation recess and at least one side recess intersecting the separation recess, wherein the separation recess and the side recess are fluidly coupled. A mixture of components is flowed through the separation recess, resulting in separated components. A labelled component-binding moiety is subsequently flown through a side recess and into the separation recess, wherein it binds to the component of interest. The component-binding moiety is then detected, thereby detecting the component of interest.

[0073] In a further embodiment the steps d and e are repeated a number of times.

[0074] This has the advantage that more label (step d) is bound to the moiety and thereby the emitted radiation in the detection steps is increased. Furthermore it allows to optimise the use of label fluid.

[0075] In a further embodiment the method for characterising or analysing at least one component that is suspected to be present in a fluid comprises,

a. introducing a fluid to be characterised or analysed in a microfluidic device according to the invention,
b. moving the fluid towards a reaction chamber,
c. combining the fluid with at least one label fluid forming a combined fluid before the reaction chamber,
d. reacting the label with the component to be characterised or analysed,

e. moving the combined fluid to the reaction chamber and reacting the label with the moiety that binds,
f. washing the reaction chamber with a washing fluid,
g. illuminating the reaction chamber to a light source emitting radiation, detecting the radiation emitted. This embodiment has the advantage that the label and component to be characterised or analysed mix and react in the fluid flow towards the reaction chamber an further inside the reaction chamber. Thereby the amount of label and/or component reacted is increased, due to improved kinetics in the flow. Further the incubation time is reduced, resulting in a shorter overall measurement time.

[0076] In a next embodiment the characterising or analysing method further comprises the use of a fluorescent of chemiluminescent label.

[0077] The separated components are typically labelled components that are optionally detected simultaneously with the component-binding moiety. This embodiment optionally includes deconvoluting the detection signal to identify the separated components and the component of interest. This embodiment includes two detectably different label moieties having detectably different spectral characteristics, such as different excitation or emission maximum. The different labels include, but are not limited to fluorescent labels, chemiluminescent labels and colorimetric labels. For example, the separated components are optionally labelled with a first fluorescent dye and the component-binding moiety is labelled with a second fluorescent dye. These two dyes are typically detectably different. In another embodiment, the component of interest and the component-binding moiety are optionally labelled with detectably different colorimetric labels. In another embodiment, the component of interest is labelled with one type of label, e.g., chemiluminescent, and the component-binding moiety is labelled with a second type of label, e.g., fluorescent.

[0078] In a further embodiment the characterising or analysing method the component to be characterised or analysed is selected from the group consisting an antibody, a cell receptor, an antigen, a receptor ligand, an enzyme, a body, an immunochemical, an immunoglobulin, a virus, a virus binding component, a protein, a cellular factor, hormones, allergenics, a growth factor, an cell-inhibitor, DNA, RNA, antigen to be bound to an antibody or receptor or a combination thereof. The fluid is preferably a body fluid, such as a blood, serum, urine, saliva, or extracts, such as plant-extracts.

[0079] In a next embodiment the characterising or analysing method further comprises the use of a laser as the light-source.

[0080] The following examples are merely meant to illustrate the invention and are not intended to limit the scope of invention in any way.

Example 1.

[0081] This example describes the measurement of myoglobin concentration in a blood sample.

[0082] A polymethylmethacrylate (PMMA)-microfluidic device containing Piezo-pumps is cleaned with ethanol (70%) followed by demineralised water. The microfluidic device is completely dried by applying compressed air. A piece of transparent foil with the same size as the microfluidic device (seals the recesses in the PMMA structure from the environment. The foil is from Permacel, a Nitto Denko company). This way the microrecesses are closed. A window in the foil was cut just over the reaction area, in order to be able to detect the light emitted by the label. The diameter of the window is 3,6 mm, of which 3,5 mm is covered with nitrocellulose. The depth of the chamber is about 450 µm.

[0083] Strips of polyester supported nitrocellulose (from Whatman) were coated with Monoclonal mouse IgG anti human Myoglobin (Medix, Finland). Spots of 1 µl (1 µg Ab/µl HEPES buffer pH 8) were dropped on to the nitrocellulose. The spots are dried at room temperature for 30 minutes. After this the nitrocellulose strips are blocked with a HEPES buffer + 0.1% Tween 20™ (from ICI, USA) at pH 8 for one hour. An additional drying step (4 hours at room temperature) is required before the strips are ready to use.

[0084] The polyester support of the nitrocellulose strip was mounted on a double-sided adhesive tape. After that the nitrocellulose side is covered with a transparent plastic foil to avoid any damage. From these strips dots of 35 mm are prepared by using a revolver punch gripper from Conrad. It should be taken into consideration that the coated antibody is in the centre of the 35 mm dot of nitrocellulose. The protection foil and the double side adhesive tape are removed, and the polyester support side is put in the centre of to a 15x10 mm piece of Permacel foil. This foil is put in the window where the reaction area is located. The nitrocellulose should face the PMMA structure, and it is located as close as possible to the outlet of the microrecess. The PMMA reaction area has a diameter of 36 mm. The reaction area is sealed with the Permacel foil containing the piece of nitrocellulose.

[0085] Using 1 ml syringes, the label and wash reservoirs are filled with their respective buffers. Both reservoirs are consisting of the chamber under the piezo-pump, the fluid diodes and the microrecesses, which are needed for a proper functioning. The label solution is a HEPES based buffer (pH8) containing a biotinylated monoclonal antibody (anti Myoglobin) with the fluorescence labelled streptavidin (Molecular Probes). The fluorescence signal is generated by a so-called Fluorescence Resonance Energy Transfer system. When the complex is excited at 635 nm it emits light at 778 nm.

[0086] After filling the reservoirs, a syringe is filled with sample (Myoglobin Std from SCIPAC (Scipac Ltd. Kent UK) diluted with HEPES buffer pH 8, at a concen-

tration of 0 ng/ml, 100 ng/ml or 1000 ng/ml respectively and connected to the sample inlet from the microfluidic device.

[0087] Piezo pumps are connected to the amplifier and the wash and label syringes were removed from the microfluidic device. At this stage, the microfluidic device was ready-to-use.

[0088] Subsequently the following steps are carried out. The syringe pump injects the sample in with 100 mseconds breaks. After 300 seconds of sample incubation the label fluid pump starts working at 3.5V (times -150) and a 0 offset with a counter pumping of the wash-buffer (amplitude 1.1 V, magnification -150 times), offset = 0, no phase shift). After 4 seconds pumping the label fluid the reaction area is incubated during 75 seconds with the label. The label fluid is refreshed seven times. This is achieved by pumping for 0,5 seconds with a 75 seconds incubation time in between each time. After the last label interval the washing pump starts to work at 3,5 V (times -150) and a 0 V offset with a counter pumping of the label (amplitude 1.0 V (times -150), offset = 0 V, no phase shift). After 5 seconds of pumping the wash-buffer the reaction area is soaked during 15 seconds. The label fluid is refreshed eight times by 0,5 seconds pumping with 15 seconds diffusion in between. The washing interval ends with 15 seconds of diffusion.

[0089] When the program is finished, the openings for the wash, label and waste fluids are sealed with Permacel foil. The sample syringe is removed and the sample inlet is also sealed with Permacel foil. The piezo-pumps are disconnected and the piece of nitrocellulose including the labelled component is removed from the reaction chamber.

[0090] The piece of nitrocellulose is placed in a strip-holder (centre position, always in the same place) of the fluorescence reader from LRE Technology Partner GmbH and kept in the dark. After drying the nitrocellulose for 30 minutes it was read out with the LRE-Reader. The reader excites the fluorescent label with a laser diode that emits at 642 nm, and a photodiode collecting the emitted light from the dye above 725 nm. The slight difference in wavelength is caused by the difference between the theoretical value and the value actually used and/or obtained. When scanning the piece of nitrocellulose the fluorescence scanner obtains one value (in arbitrary fluorescence units) every 0.054 mm.

[0091] In figure 7 the results of the measurement are shown. The first three peaks are three assays done on the same body, which were incubated with 0, 100, and 1000 ng/ml of Myoglobin, successively. The second part of the figure shows a group of three peaks under identical conditions but on another body. The detector determines the peak width. The detector scans the nitrocellulose, each time generating a signal.

[0092] Going from left to right the maximum peak level increases with Myoglobin concentration. As the spots used were placed as a liquid on the nitrocellulose the peaks can be somewhat α-symmetrical. The second series is somewhat different with respect to peak (height and width) as compared to the first series, which is due to statistical variation and reproducibility.

Example 2.

[0093] The microfluidic device according to the present invention is produced by methods known to the person skilled in the art.

[0094] An embodiment according to the invention consists out of a PMMA body (see figure 4). Figure 4 shows the layout, though the dimensions shown herein are different in reality. The size of this body is 60 by 47 by 1 mm^3. The recesses in the front side and back side of the body are manufactured by injection-moulding the PMMA body. Also the fluid diodes are made by injection moulding. The width of the fluid connections is about 1 mm, the depth is approximately 450 μm. The diameter of the reaction chamber is about 4 mm.

[0095] The body consists out of one provision for an inlet. Also three provisions for an outlet are present, the first in connection with the meandering fluid path with the wash fluid, the second in connection with the meandering fluid path for collecting the waste fluid, and the third in connection with the meandering fluid path with the label fluid. It further contains fluid connections between the provision for the inlet and the reaction chamber, between the meandering fluid path for collecting the waste fluid and the reaction chamber, between the meandering fluid path with the wash fluid and the reaction chamber and between the meandering fluid path with the label fluid and the reaction chamber. Also is contains two pump chambers, one for pumping the label fluid and one for pumping the wash fluid. These pump chambers are connected to the wash fluid and label fluid by a fluid connection from one side of the body to the other. Further four fluid diodes are present for directing the fluid.

[0096] The cover layers are connected to the body by hot-welding PMMA. Before this hot-welding step a strip of nitrocellulose was place on the covering PMMA layer, in a location that it coincides with the reaction chamber. The reaction chamber contains as a moiety monoclonal mouse IgG anti human Myoglobin.

[0097] This moiety was deposited on the cover layer prior to the hot-welding step. A drop of fluid containing the moiety was dripped on the nitrocellulose strip, of which the location also coincides with the reaction chamber.

[0098] The pumps used are readily available piezo-pumps.

[0099] The wash fluid used is demineralised water. The label fluid solution is a HEPES based buffer (pH 8) containing a biotinylated monoclonal antibody (anti Myoglobin) with the fluorescence labelled streptavidin (Molecular Probes).

Example 3

[0100] A preferred embodiment of the characterising or analysing device is constructed out of components that are readily available.

[0101] The housing of the measurement device can be constructed by injection-moulding. The material used in the housing can be typically a polymer.

[0102] The communication ports used can be standard USB-interfaces, consisting out of USB-plugs and USB-sockets.

[0103] The read-in unit can be a standard chip-read-out unit, used for instance for banking-cards, which is widely available.

[0104] The receiving device can be a standard receiving unit, used for instance for the intake of banking-cards in an ATM, which is widely available.

[0105] Typically the measurement device contains a laser. A preferred laser can be a standard 635 nm laser, which is widely available. The type of laser and frequency used will clearly depend on the component that is suspected to be present and/or the label used.

[0106] The detection unit can be a standard 778 nm detection unit, which is widely available.

[0107] Typical voltage amplitudes applied to the piezo-pump are 150V and 300V. The achieved pressure is from 200 to 4000 Pa, but may vary upon the piezo-pump used, the type of fluid diode and pumping altitude.

[0108] The information unit can be a standard LCD-display, which is widely available.

Claims

1. System for characterising or analysing a fluid, which fluid is suspected to comprise at least one component to be characterised or analysed, comprising a microfluidic device, at least one pump for transporting the fluid and a measurement device which is arranged to characterise or analyse the at least one component in the microfluidic device,
   which microfluidic device comprises at least one body(11), wherein the body has at least one surface, wherein the at least one surface has at least a part of the recess for containing the fluid in the microfluidic device and/or transporting the fluid in the microfluidic device through at least a part of the microfluidic device,
   wherein the body has at least one provision for an inlet (15) and at least one provision for an outlet (18),
   wherein at least a part of said recess (16) is a reaction chamber, which reaction chamber comprises a moiety that binds to the at least one component that is suspected to be present and that is to be characterised or analysed, which reaction chamber is arranged for characterising or analysing the at least one component,
   wherein at least a part of said recess is a fluid connection (14) between the at least one provision for an inlet (15) and the at least one provision for an outlet,
   wherein at least a part of said recess (17) is a pump chamber,
   wherein at least the reaction chamber, pump chamber and fluid connection are sealed from the environment by at least one cover layer (12, 13).

2. A system according to claim 1, where the measurement device comprises a measurement device for characterising the fluid, wherein the measurement device is arranged to obtain information based on an optical technique selected from the group consisting of fluorescence, chemiluminescence, time resolved fluorescence, time resolved chemiluminescence, colorimetry or a combination thereof, or from the group consisting of magnetic measurements, resistivity measurements, capacity measurements, surface plasma resonance (SPR) measurements, or a combination thereof.

3. A system according to anyone of claims 1-2, wherein the characteristics of the fluid comprise a concentration of at least one of the components of the fluid.

4. A system according to anyone of claims 1-3, wherein the at least one pump is a piezo-pump.

5. A system according to anyone of claims 1-4, which is a disposable.

6. Microfluidic device arranged for use in the system of anyone of the preceding claims, which microfluidic device comprises at least one body (11), wherein the body has at least one surface, wherein the at least one surface has at least a part of the recess for containing the fluid in the microfluidic device and/or transporting the fluid in the microfluidic device through at least a part of the microfluidic device,
   wherein the body has at least one provision for an inlet (15) and at least one provision for an outlet (18),
   wherein at least a part of said recess (16) is a reaction chamber, which reaction chamber comprises a moiety that binds to the at least one component that is suspected to be present and that is to be characterised or analysed, which reaction chamber is arranged for characterising or analysing the at least one component,
   wherein at least a part of said recess is a fluid connection (14) between the at least one provision for an inlet (15) and the at least one provision for an outlet,
   wherein at least a part of said recess (17) is a pump chamber,

wherein at least the reaction chamber, pump chamber and fluid connection are sealed from the environment by at least one cover layer (12, 13).

7. Microfluidic device according claim 6, wherein one cover layer and another cover layer form together one part.

8. Microfluidic device according to anyone of claims 6 or 7, which further comprises a filter in the at least one provision for an inlet.

9. Microfluidic device according to anyone of claims 6-8, further comprising

a. at least a part of the recess for a washing fluid, and
b. at least a part of the recess for collecting waste fluid.

10. Microfluidic device according to anyone of claims 6-9, which further comprises at least a part of the recess which comprises at least one label fluid, which label binds to the moiety in the reaction chamber and/or to the at least one component to be characterised or analysed.

11. A microfluidic device according to anyone of claims 6-10, which comprises at least one provision for an inlet (15) which is arranged to receive the fluid, said inlet being sealed by a seal from the environment, which seal is to be removed upon use, thereby opening at least one entrance to the at least one provision for an inlet and/or which comprises at least one provision for an outlet (18) that is prior to use sealed from the environment by a seal, which seal is to be removed upon use.

12. A microfluidic device according to anyone of claims 6-11, which comprises at least one soft seal that closes at least a part of the recess.

13. The microfluidic device according to anyone of the claims 6-12, **characterized in that** at least one of the fluid connection(s) is equipped with fluid diodes for resisting a flow of the fluid through the fluid connections in one direction.

14. The microfluidic device according to claim 13, wherein the fluid diodes have a brush-like or a valve-like structure.

15. The microfluidic device according to anyone of the claims 6-14, wherein the moiety that binds is chosen from the group consisting of a nuclear receptor, an intracellular receptor, a solubilized receptor, an antibody, an antigen, an enzyme, avidin, a polynucleotide and a polysaccharide.

16. The microfluidic device according to anyone of the claims 6-15, which further comprises elements for directing the fluid.

17. The microfluidic device according to anyone of the claims 6-16, which further comprises a readable information carrier.

18. The microfluidic device according to anyone of the claim 10 or claims 11-17 dependent thereon, wherein the at least one label is selected from the group consisting fluorescent labels, chemiluminescent labels and colorimetric labels.

19. Measurement device suitable for use in a system according to anyone of claims 1-5, for characterising or analysing a fluid in the microfluidic device of anyone of claims 6-18, which fluid is suspected to comprise at least one component to be characterised or analysed, comprising a characterising or analysing apparatus to be associated to the microfluidic device.

20. The measurement device according to claim 19, which further comprises,

a. at least one communication port for transferring data,
b. at least one read-out unit for reading in characteristics of the microfluidic device,
c. at least one light source illuminating the reaction chamber in the microfluidic device,
d. at least one detection element for detecting the radiation emitted from the reaction chamber,
e. an information unit displaying characteristics of the fluid.

21. Measurement device according to claim 20, wherein the communication port is of an USB-type.

22. Measurement device according to anyone of the claims 20-21, wherein the read-out unit is of a chip-reader

23. Measurement device according to anyone of the claims 20-22, wherein the light source is a laser.

24. Measurement device according to anyone of the claims 20-23, wherein the detection element is a photodiode is, a CCD, a photo multiplier tube (PMT) or a series of photodiodes.

25. Measurement device according to anyone of the claims 20-24, which comprises software.

26. Method for characterising or analysing at least one component that is suspected to be present in a fluid

comprising,

a. introducing a fluid to be characterised or analysed in a microfluidic device according to anyone of claims 6-18,
b. moving the fluid to a reaction chamber,
c. reacting the fluid with the moiety that binds,
d. moving a washing fluid to the reaction chamber and washing the reaction chamber,
e. illuminating the reaction chamber to a light source emitting radiation,
f. detecting the radiation emitted.

27. Method for characterising or analysing at least one component that is suspected to be present in a fluid comprising according to claim 26, which further comprises between steps c) and d), the step

a. moving a label fluid to the reaction chamber and reacting the label with the moiety that binds and/or with the component to be

characterised or analysed.

28. A characterising or analysing method according to claim 27, wherein steps d and e are repeated a number of times.

29. Method for characterising or analysing at least one component that is suspected to be present in a fluid comprising,

a. introducing a fluid to be characterised or analysed in a microfluidic device according to anyone of claims 6-18,
b. moving the fluid towards a reaction chamber,
c. combining the fluid with at least one label fluid forming a combined fluid before the reaction chamber,
d. reacting the label with the component to be characterised or analysed,
e. moving the combined fluid to the reaction chamber and reacting the label with the moiety that binds,
f. washing the reaction chamber with a washing fluid,
g. illuminating the reaction chamber to a light source emitting radiation,
h. detecting the radiation emitted.

30. A characterising or analysing method according to anyone of claims 26-29, wherein the label is fluorescent, colorimetric or chemiluminescent.

31. A characterising or analysing method according anyone of the claims 26-30, wherein the light-source is a laser.

32. A characterising or analysing method according anyone of the claims 26-31, where the component to be characterised or analysed is selected from the group consisting an antibody, a cell receptor, an antigen, a receptor ligand, an enzyme, a body, an immunochemical, an immunoglobulin, a virus, a virus binding component, hormones, allergenics, a protein, a cellular factor, a growth factor, an cell-inhibitor, DNA, RNA, antigen to be bond to an anti-body or receptor or a combination thereof.

33. Method of pumping, applicable in anyone of claims 27-32, which comprises the step of

a. at least two intervals of pumping of at least a fluid and a pause time in between pumping.

34. A method of pumping according to claim 33, which further comprises a sequence of pumping of at least a fluid and at least another fluid.

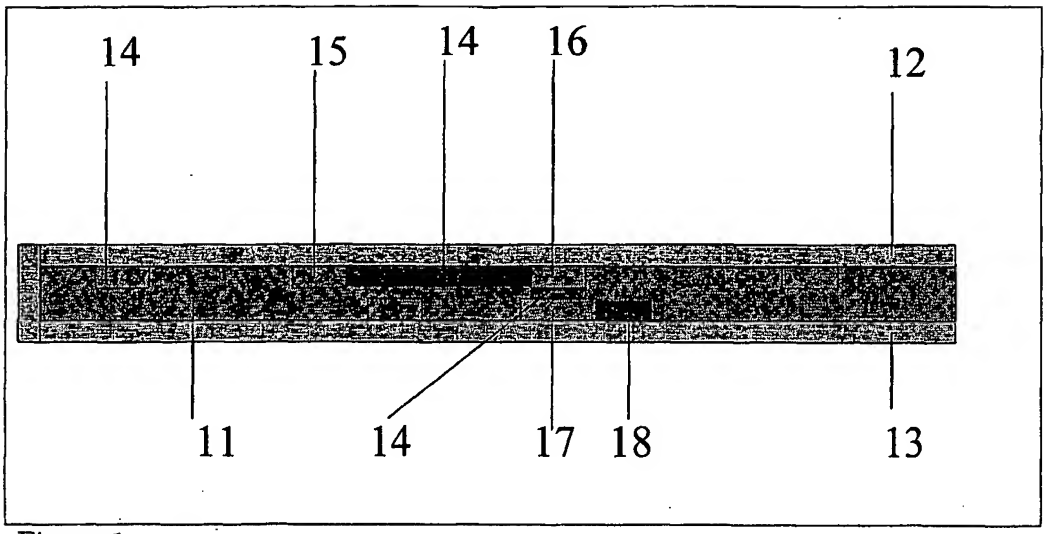

Figure 1

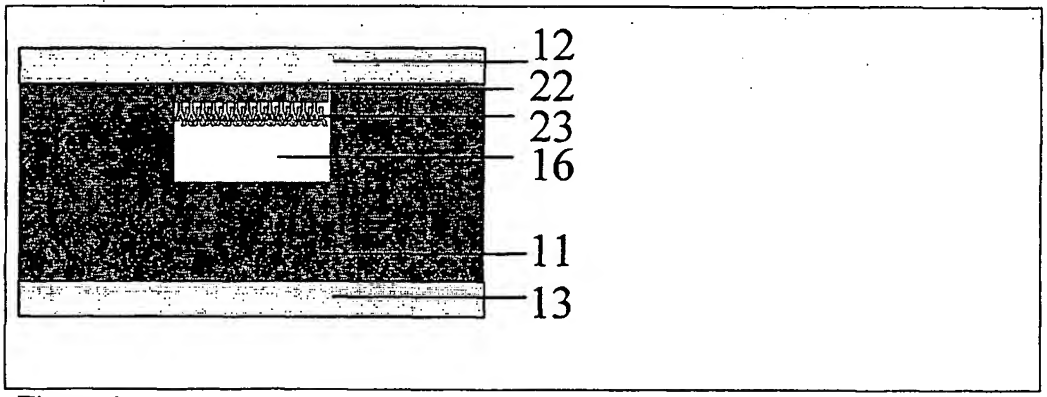

Figure 2

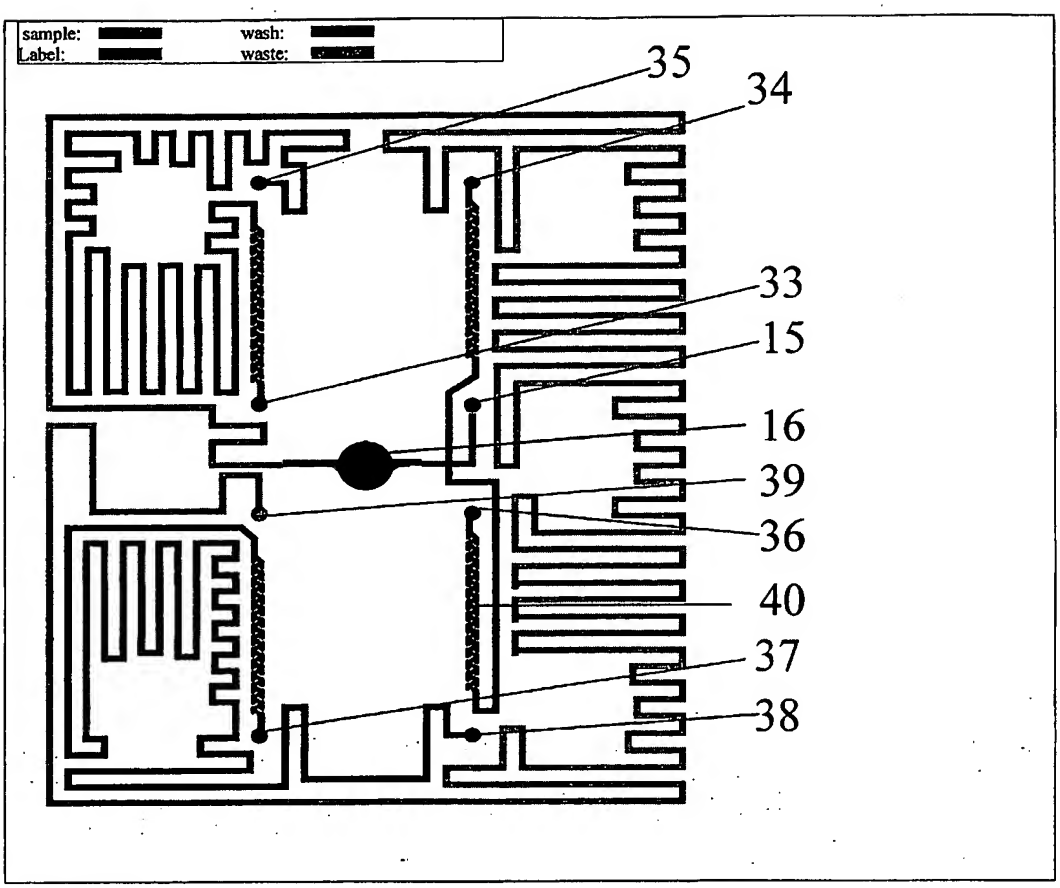

Figure 3

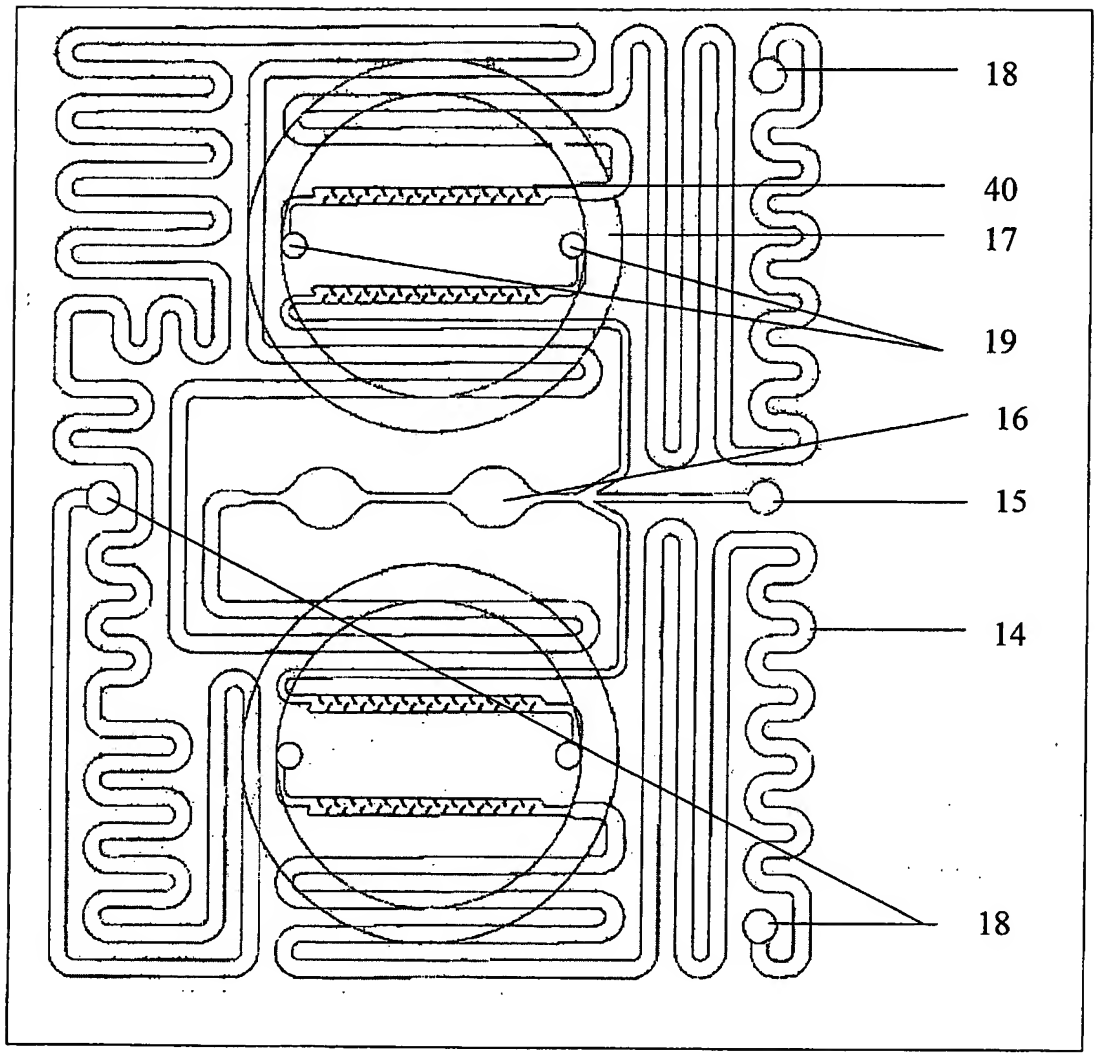

Figure 4

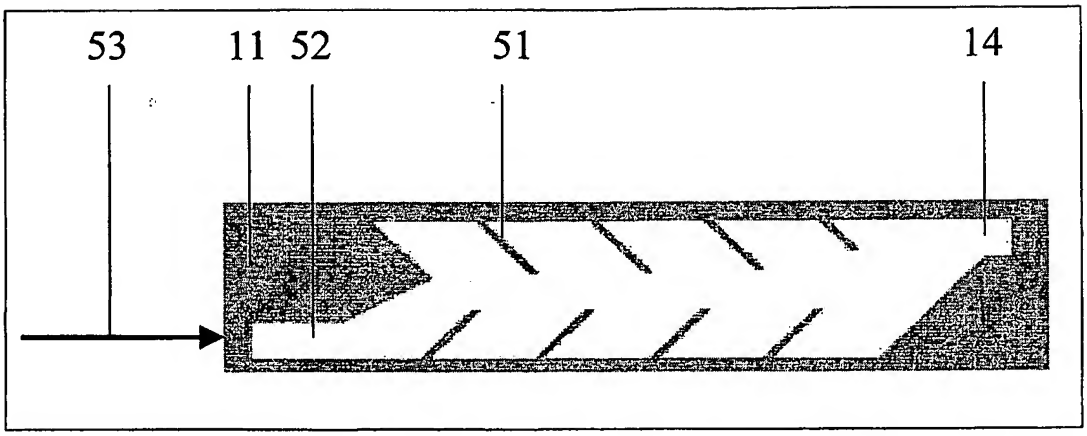

Figure 5

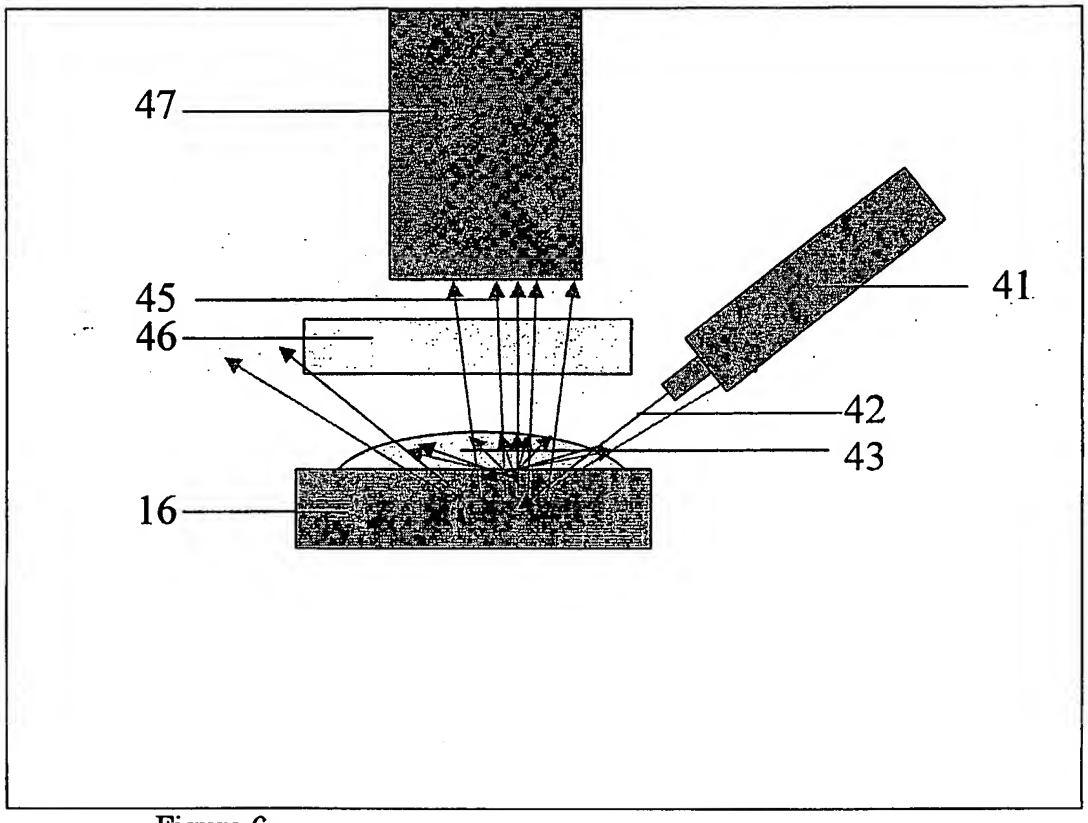

Figure 6

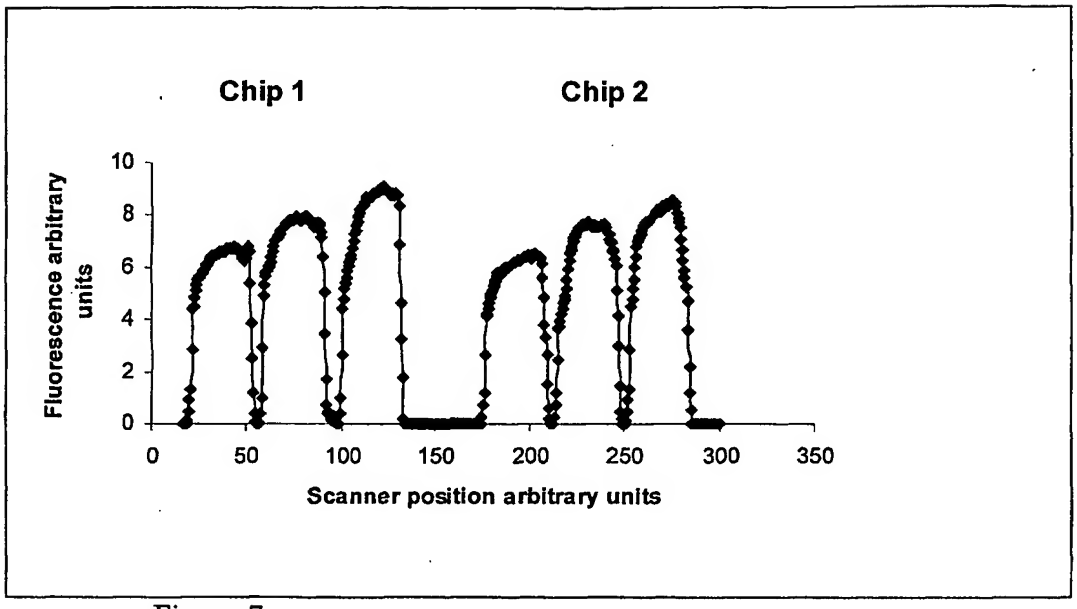
Chip 1
Chip 2
Fluorescence arbitrary units
10
8
6
4
2
0
0
50
100
150
200
250
300
350
Scanner position arbitrary units

Figure 7

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 04 07 5257

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 2002/123059 A1 (HO WINSTON Z) 5 September 2002 (2002-09-05) * paragraph [0020] - paragraph [0032] * * abstract * * claims * * figures * -----	1-7, 9-12, 15-20, 23-32	B01J19/00 B01L3/00

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

B01J
B01L
G01N

~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
Munich	29 June 2004	Smith-Hewitt, L

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

Application Number
EP 04 07 5257

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-7, 9-12, 15-20, 23-32

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 04 07 5257

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-7,9-12,15-20,23-32

a microfluidic device comprising at least one body wherein the body has at least one surface wherein the at least one surface has at least a part of a recess for containing the fluid in the device and transporting the fluid in said device through at least a part of said device wherein the body has at least one provision for an inlet and at least one provision for an outlet wherein part of the recess is a reaction chamber, which comprises a moiety that binds to the component(s) suspected to be present and to be characterised or analysed, the reaction chamber is arranged for characterising or analysing the component, at least a part of the recess is a fluid connection between the at least one provision for an inlet and the at least one provision for an outlet, at least a part of the recess is a pump chamber and the reaction chamber, pump chamber and fluid connection are sealed from the environment by at least one cover layer. System and method using the device. Measurement device for said microfluidic device.

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2. claim: 8

A microfluidic device comprising a filter in the provision for an inlet.

---

3. claims: 13, 14 (e.g. when dependent on claims 6 and 7)

The fluid connection(s) on a microfluidic device are equipped with fluid diodes

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4. claim: 21

The communication port of a measurement device is a USB port

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5. claim: 22

The read out unit is a chip reader

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6. claims: 33,34

a method of pumping comprising the step of at least two intervals of pumping of at least a fluid and a pause time in between pumping.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 04 07 5257

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

29-06-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002123059 A1	05-09-2002	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82